PAPERS AND ORIGINALS

Experience with Simplified Scheme of Treatment of Hyperlipidaemia

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Summary

A series of 57 hyperlipidaemic patients have been investigated clinically and by measurement of cholesterol and triglyceride levels and inspection of stored serum. Two had secondary (alcoholic) hyperlipidaemia. Those with primary disorders were allocated to three groups believed to require different optimal therapy. At one year 51 of these 55 patients had lipid levels within a predetermined normal range and two others showed improvement. Despite the large number of primary hyperlipidaemic states our results suggest that in most patients successful treatment can be given according to simple classification into three therapeutic categories.

Introduction

The main rationale for treatment of hyperlipidaemia is the association between abnormally high plasma cholesterol and triglyceride concentrations and ischaemic heart disease (Keys, 1970; Goldstein *et al.*, 1973). Though the significance of this association has been reinforced by prospective studies showing that raised cholesterol and triglyceride levels are predictive of ischaemic heart disease (Stamler, 1967; Carlson and Bottiger, 1972) rigorous proof is lacking that the association is causal. Nevertheless, it is now common clinical practice to attempt to correct hyperlipidaemia, and this practice obtains further justification from the encouraging results of the "first generation" trials of serum lipid reduction in the primary

prevention of ischaemic heart disease (Christakis *et al.*, 1966; Stamler *et al.*, 1968; Dayton *et al.*, 1969; Miettinen *et al.*, 1972) and of some (Leren, 1970; Dewar, 1971; Oliver, 1971) but not all (Morris, 1968) trials of secondary prevention—that is of relapse. Animal experimental evidence that diet-induced hyperlipidaemia leads to atherosclerosis-like lesions has existed for two-thirds of a century, and recent suggestions have been made that such lesions are partly reversible by lipid-lowering regimens (Armstrong and Megan, 1972).

Apart from the risk of ischaemic heart disease and peripheral vascular disease the correction of hyperlipidaemia is sometimes called for to treat or prevent disfiguring xanthomas, acute abdominal pain and recurrent pancreatitis, and some rheumatological complications of raised lipid levels.

In 1968 a lipid clinic was started at Hammersmith Hospital by Dr. N. B. Myant and one of us (B.L.) for the investigation and management of hyperlipidaemic states. A major stimulus to the setting up of the clinic was provided by the development of a new classification of hyperlipidaemia by Fredrickson *et al.* (1967). This classification into five types, later increased to six, provided valuable clarification of this heterogeneous group of disorders. Recently we have attempted to classify our patients with primary hyperlipidaemia into three therapeutic categories (Lewis, 1973). This was not intended as a fundamental classification but was performed in order to allocate patients to a minimum number of groups believed to require different optimal therapy.

We here report our experience of treating a pilot group of 57 consecutive hyperlipidaemic patients at the clinic.

Patients and Methods

Hyperlipidaemia was detected in the course of investigating patients with ischaemic heart disease or peripheral vascular disease, xanthomas, or abdominal pain or by investigation of the relatives of patients with raised serum lipids. Other patients were referred after hyperlipidaemia was recognized during health screening by the B.U.P.A. Medical Centre. Adult patients with either serum cholesterol concentrations of 300 mg or more/100 ml or serum triglyceride levels of 180 mg or more/100 ml or both in two fasting samples

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qualified for inclusion in the series. This report is on 57 patients referred between May and August 1972. Their serum cholesterol levels ranged from 310 to 580 mg/100 ml and their triglyceride concentrations from 205 to 10,400 mg/100 ml.

LABORATORY PROCEDURES

Blood was drawn without stasis after the patients had fasted for 14 hours. Cholesterol and triglyceride were measured by standard semi-automated procedures (Technicon N-24a; Technicon N-78; Cramp and Robertson, 1968). A serum sample was stored for 18 hours at 4°C and inspected for floating opalescence (indicating the presence of chylomicra) and for diffusely distributed opalescence (indicating abnormally raised levels of prebetalipoprotein or of the "broad-beta" lipoprotein). The results were reported to the clinician.

In addition the lipoprotein pattern in fasting serum was analysed by electrophoresis on cellulose acetate using fat red 7B stain and also, where indicated, by preparative ultracentrifugation (Hatch and Lees, 1968) with lipid analyses and electrophoresis of the fractions. These results were not reported to the lipid clinic but were monitored by one of us (S.T.) and were correlated at the end of the study with the patients' response to treatment.

TREATMENT

Most patients were managed as outpatients but some were admitted for investigation and for initiation of therapy. The diagnosis of alcoholic lipidaemia was established by observing the effect of withdrawal of alcohol under observation in the ward. The lipid clinic is held weekly, the staff including a dietitian. Patients reattending initially at intervals of two to three weeks. When hyperlipidaemia is corrected they are followed up at intervals of six to 12 months.

The therapeutic classification of the patients was based on the clinical findings, the serum level of cholesterol and triglyceride, and the appearance of stored serum together with investigations chiefly intended to identify causes of secondary hyperlipidaemias—for example, thyroid function tests and thyroid-stimulating hormone assay, serum gammaglutamyl transpeptidase and other liver function investigations, and measurement of glucose and uric acid levels and of serum proteins. Glucose tolerance tests were not routinely performed.

Underlying causes of hyperlipidaemia were identified in only two patients; this is probably less than the usual frequency of secondary hyperlipidaemia and reflects also the fact that diabetics are not managed at the lipid clinic.

The patients with primary abnormalities of lipid metabolism were divided into the following three groups:

(1) Hypercholesterolaemia (serum cholesterol > 300 mg/100 ml, serum triglyceride < 180 mg/100 ml, clear fasting serum). Four patients had tendon xanthomas; 28 patients were allocated to this group.

(2) Endogenous hypertriglyceridaemia (serum triglyceride > 180 mg/100 ml, serum cholesterol < 300 mg/100 ml, diffuse opalescence in stored serum). Eleven patients were allocated to this group.

(3) Hypertriglyceridaemia of exogenous origin (serum triglycerides > 180 mg/100 ml, floating opalescence and clear supernatant in stored serum). No patient's serum had the characteristics of this rare disorder in the present series.

A combination of these characteristics, with raised levels of both cholesterol and triglyceride, occurred in 16 patients. The management of patients in these groups was as follows.

Secondary Hyperlipidaemia

In patients with secondary hyperlipidaemia treatment was directed to the underlying cause; in this series there were two patients, both with alcoholic hyperlipidaemia.

Primary Hyperlipidaemia

Group 1.—A modified-fat, low cholesterol diet (fat calories 32%, ratio of polyunsaturated to saturated fat 1.4:1, cholesterol 300 mg/day) was prescribed for all patients. In patients with initial serum cholesterol levels exceeding 330 mg/100 ml and in those whose cholesterol level was not reduced adequately by diet, treatment with cholestyramine, dextrothyroxine, nicotinic acid, or neomycin was added. Drug therapy was often required. All patients with tendon xanthomas needed a lipid-lowering drug. The most widely used drug was cholestyramine 20-32 g/day. Dextrothyroxine 6-8 mg/day was given to four patients, together with propranolol 20 mg three times daily or practolol 100 mg twice daily (Krikler *et al.*, 1971) to minimize possible thyrocardiac side effects. Criteria for use of dextrothyroxine were freedom from clinical and E.C.G. evidence of ischaemic heart disease and age less than 40 years. In practice it was considered in patients who developed troublesome constipation or dyspepsia as side effects of cholestyramine therapy. Nicotinic acid and neomycin were rarely used, as second-line drugs, for patients who had responded incompletely to diet and cholestyramine.

Group 2.—A reducing diet (600, 800, or 1,000 k/cal) was prescribed for all patients with even mild obesity, aiming to maintain a weight in the middle of the desirable body weight range (Metropolitan Life Insurance Company, 1959); a modified-fat, low-cholesterol diet was prescribed in initially lean patients and in patients with hypertriglyceridaemia persisting after weight reduction. Clofibrate 1 g twice daily was prescribed for the few patients who failed to respond to or were unable to adhere to dietary treatment.

Group 3.—Treatment would comprise low intake of fat containing long-chain fatty acids and partial replacement with medium-chain triglyceride.

Combined Hyperlipidaemia

Patients with combined hyperlipidaemia were treated initially in the same way as those in group 2, except for two who had tendon xanthomas; they were given drug treatment as for group 1.

Results

The relation between the therapeutic groupings and the formal lipoprotein typing based on electrophoresis or ultracentrifugation is shown in table I. Both patients with secondary hyperlipidaemia had the type V lipoprotein pattern due to alcoholism. Neither glycosuria nor fasting hyperglycaemia was observed, possibly due to prior exclusion of diabetics by referring doctors.

TABLE I—Numbers of Patients in Therapeutic Groups divided according to W.H.O. Lipoprotein Typing System

Group	W.H.O. Type					Total
	IIa	IIb	III	IV	V	
1	28					28
2		12	1	11		11
Combined				3		3
Secondary					2	2
Total	28	12	1	14	2	57

No patient was allocated to group 3—that is, no patient had the type I lipoprotein pattern.

Few group 1 patients were obese; the average pretreatment weight was 70 kg in men and 62 kg in women, with an average loss during treatment of 1.9 kg. By contrast most patients in group 2 and most patients with combined hyperlipidaemia were obese; their average weights on presentation were, respectively, 78 and 80 kg in men and 77 and 66 kg in women. During treatment an average weight loss of 10 kg was obtained both in group 2 patients and in those with combined hyperlipidaemia.

The results of treatment for one year, with a follow-up period of a further five months, are shown in table II. The predetermined upper limits of normal were for serum cholesterol 270 mg/100 ml and for serum triglyceride concentration 160 mg/100 ml. These values were lower than the 95th percentiles for an apparently healthy London population (Lewis *et al.*, 1974).

TABLE II—Numbers of Patients in Therapeutic Groups attaining Normal Lipid Levels (Total Numbers in Parentheses)

Group	W.H.O. Type					Total
	IIa	IIb	III	IV	V	
1	26 (28)			11 (11)		26 (28)
2		10 (12)	1 (1)	3 (3)		11 (11)
Combined					0 (2)	14 (16)
Secondary						0 (2)
Total	26 (28)	10 (12)	1 (1)	14 (14)	0 (2)	51 (57)

By these criteria 51 of the 57 patients achieved normal serum lipid levels in at least three consecutive samples. The time required to obtain acceptable lipid concentrations, however, varied from less than three months to one year and differed for the various therapeutic groups. In 10 out of 14 patients with raised prebetalipoprotein levels (mainly group 2) the hypertriglyceridaemia was corrected within three months and all were normal within six months, but treatment of patients with raised betalipoprotein levels took longer. They were allocated to group 1 or the combined category and had the type IIa or IIb lipoprotein pattern. Sixteen out of 40 patients had normal cholesterol levels within three months, 31 within six months, and 36 by one year. The patient with the "broad-beta" lipoprotein abnormality (type III) achieved normal lipid levels within three months but retained the qualitatively abnormal band on electrophoresis; her palmar xanthomas, which are highly suggestive of this lipoprotein abnormality, cleared within the same period.

Of the six patients in whom cholesterol or triglyceride levels or both were still raised at one year four showed substantial improvement with at least a 40% reduction in lipid levels. All had a severe degree of hyperlipidaemia before treatment. The patients with alcoholic hyperlipidaemia attained normal lipid levels during alcohol withdrawal in the ward but both partially relapsed as outpatients; at one year triglyceride concentrations showed 85% and 60% reductions compared with pretreatment values. Of the other two patients with improved but still hyperlipidaemic sera one had the type IIa pattern and the other the type IIb.

Two further patients showed no improvement on pretreatment lipid levels after one year. One who had combined hyperlipidaemia (lipoprotein type IIb) did not respond to dietary treatment and did not adhere to his medication. In other patient, treated by diet and with cholestyramine according to group 1 (lipoprotein type IIa), the hyperbetalipoproteinaemia improved but she developed raised levels of prebetalipoprotein (type IV) at nine months and a year. She was later treated with the addition of clofibrate.

Discussion

Of the 57 patients in this series 51 attained acceptable serum lipid levels and four others showed marked reduction of their

hyperlipidaemia. This was achieved using two out of three therapeutic categories, for "pure" hypercholesterolaemia and "pure" endogenous hypertriglyceridaemia; the third category (exogenous hypertriglyceridaemia) was not represented in this series. One-third of the patients had a combination of the first two of these lipid abnormalities. Two features of this approach may be noted. Allocation to the three categories was based on clinical data together with simple laboratory tests. Measurement of cholesterol and triglyceride concentration by manual or automated methods is within the reach of all hospital laboratories, and the qualitative procedure, inspection of stored serum, requires a little experience but is essentially a clinic-room procedure. Secondly, the range of treatments is rationalized; in particular, only three diets are used, compared with six (including the weight-reducing regimens) designed by the National Heart and Lung Institute (1971).

Though the six-type W.H.O. classification of hyperlipidaemia (Beaumont *et al.*, 1970) (based on abnormalities of serum lipoprotein patterns) is, with justification, most extensively used at present it is, together with several related systems, a provisional attempt to distinguish clinical and therapeutic entities. No aetiological classification is as yet possible. Genetic analysis of serum lipids in survivors of myocardial infarction and their relatives has suggested the existence of four genetically determined hyperlipidaemic states which do not conform to the six W.H.O. types (Goldstein *et al.*, 1973). Probably no current system encompasses all forms of primary hyperlipidaemia; raised lipid levels may occur, not only in the six W.H.O. types but in hyperalphalipoproteinaemia (Carlson and Kolmodin-Hedman, 1972), alphalipoprotein deficiency (Tangier disease) (Lloyd, 1973), and lecithin: cholesterol acyl-transferase deficiency (Norum *et al.*, 1972), and an increasing number of secondary hyperlipidaemic states are being recognized.

Though most of our patients responded satisfactorily to treatment the reduction, particularly of raised betalipoprotein levels, was often slow. The rare homozygous form of hyperbetalipoproteinaemia (not seen in the present series) is not always fully corrected even by heroic surgical measures (Moore *et al.*, 1973; Starzl *et al.*, 1973). There is a need for improved cholesterol-lowering drugs and for better understanding of the indications for the several existing drugs, alone and in combination.

The reasonably satisfactory results obtained in this series partly reflect the type of hyperlipidaemic patient referred to a lipid clinic operating in a general hospital. Many presented with complications of atherosclerosis or were asymptomatic relatives of patients with hyperlipidaemia. Most hypercholesterolaemic patients had moderate rather than extreme increases in lipid levels and relatively few had tendon xanthomas. Another factor influencing the success rate was the choice of upper limits of normal. While the predetermined upper limits for cholesterol and triglyceride are in common use it is conceivable that more ambitious targets should be set if the progress of atherosclerosis is to be halted. The results also reflect the generally high degree of dietary adherence by patients, probably related to their frequent initial attendance at the clinic.

A further therapeutic problem, seen in only one of our patients, is that correction of one form of hyperlipoproteinaemia is sometimes followed by increased levels of other lipoproteins. Reduction in betalipoprotein cholesterol level by cholestyramine may be associated with a rise in triglyceride levels due to a high prebetalipoprotein level (Jones and Dobrilovic, 1970); and correction of severe hypertriglyceridaemia by clofibrate may be accompanied by raised betalipoprotein levels (Strisower *et al.*, 1968; Wilson and Lees, 1972). The mechanism of these iatrogenic effects is uncertain. It does not to our knowledge occur when hyperlipidaemia is treated by the modified-fat, low-cholesterol diet, which is in this respect preferable to drug treatment.

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Malabsorption in Overland Travellers to India

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Summary

Thirty-four cases of malabsorption are described in young adults after brief periods of overland travel to India. Symptoms included diarrhoea, abdominal distension, and weight loss. Investigation revealed fat, xylose, and vitamin B₁₂ malabsorption with marked morphological changes in the mucosa. Lower levels of serum folate and vitamin B₁₂ were observed in those with protracted diarrhoea, but no anaemia developed. Malabsorption may persist for many months after return to the U.K. Most patients responded initially to antibiotics, but some subsequently relapsed. The reasons why these patients developed tropical sprue are discussed.

Introduction

Malabsorption occurring in expatriates living in the tropics for short periods of time has been described in Peace Corps volunteers in Pakistan (Lindenbaum *et al.*, 1966) and in military personnel in Singapore (O'Brien and England, 1971) and Vietnam (Sheehy *et al.*, 1965). Malabsorption may also occur occasionally after a variety of infective enteritis contracted outside the tropics (Montgomery *et al.*, 1973).

In the last decade overland travel, particularly to the sub-continent of India, has become increasingly popular. We report clinical findings in 34 travellers who developed persistent malabsorption during their journey.

Patients

The 28 men and six women had a mean age of 25 (range 19-39 years). All were Caucasian but of different nationalities—23 Britons, five North Americans, four Australasians, and two South Africans. Patients were all seen initially as out-patients; only those who completed all the necessary investigations of malabsorption were included in the series.

They had had symptoms of diarrhoea for between one and nine months and evidence of malabsorption consistent with the definition of tropical sprue agreed by the Wellcome Trust Collaborative Studies (Mathan and Baker, 1971; Mollin and Booth, 1971; O'Brien and England, 1971). Patients were not included in this series if they were found to have gluten enteropathy, Crohn's disease, or other anatomical or immunological bowel disorders. Patients were also excluded if they had infection with *Giardia lamblia*, *Strongyloides stercoralis*, or *Ascaris lumbricoides*.

The 34 patients included in the series were all healthy and of normal weight before their overland journey. They nearly all undertook their journey as a holiday or as part of an attempt to change their way of life; only one man travelled for business reasons. Though the availability of marijuana was an undoubted attraction no patient was known to be addicted to alcohol or drugs taken by injection either before or after his journey. Very few travelled by one means of transport; most journeyed partly by foot, donkey, truck, bus, or train and often linked up with other groups of young wandering Caucasians. Most were on limited budgets and ate the same food and drank the same water as that taken by the indigenous population. Only rarely was this supplemented by the additional purchase of meat or fresh vegetables as both commodities were relatively expensive and often unobtainable.

The route most commonly taken and the main areas where the initial bout of severe diarrhoea occurred are shown in fig. 1. Diarrhoea most frequently started in Kabul and Katmandu, but these were probably the two most commonly visited towns and not necessarily those in which tropical sprue is particularly likely to develop. Two patients in the series developed their diarrhoea in north-west Africa.

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